

REVIEW ARTICLE

Nutrigenetics and nutraceuticals: the next wave riding on personalized medicine

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The Human Genome Project and subsequent identification of single nucleotide polymorphisms (SNPs) within populations has played a major role in predicting individual response to drugs (pharmacogenetics) leading to the concept of “personalized medicine.” Nutritional genomics is a recent off-shoot of this genetic revolution that includes (1) nutrigenomics: the study of interaction of dietary components with the genome and the resulting proteomic and metabolomic changes; and (2) nutrigenetics: understanding the gene-based differences in response to dietary components and developing nutraceuticals that are most compatible with health based on individual genetic makeup. Despite the extensive data on genetic polymorphisms in humans, its translation into medical practice has been slow because of the time required to accumulate population data on SNP incidence, understand the significance of a given SNP in disease, and develop suitable diagnostic tests. Nutrigenomics revitalized the field by showing that nutrients and botanicals can interact with the genome and modify subsequent gene expression, which has provided a great impetus for nutrigenetic research and nutraceutical development based on nutrigenetics. Polymorphisms in methylene tetrahydrofolate reductase (MTHFR) (involved in folate metabolism), apolipoprotein E (Apo E) and ApoA1 (in cardiovascular disease), and leptin/leptin receptor (obesity) genes are some good examples for understanding basic nutrigenetics. Developing nutraceuticals to prevent and manage thrombosis risk in women with thrombophilic gene mutations are discussed in the context of the opportunities that exist at the nutrigenetic/pharmacogenetic interphase leading to “personalized nutrition.” Further research on individual differences in genetic profiles and nutrient requirements will help establish nutrigenetics as an essential discipline for nutrition and dietetics practice. (Translational Research 2007;149:55–61)

Abbreviations: Apo E = apolipoprotein E; CAM = complimentary and alternative medicine; CHD = coronary heart disease; HDL = high-density lipoprotein; HRT = hormone replacement therapy; LDL = low-density lipoprotein; MTHFR = methylene tetrahydrofolate reductase; PAI-1 = plasminogen activator inhibitor; SNP = single nucleotide polymorphism; WHI = Women’s Health Initiative

The completion of the Human Genome Project¹ has sparked a great deal of research on individual variation in gene sequences, particularly in single nucleotide polymorphisms (SNPs), their role in chronic diseases, and in predicting individual responses to drugs

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(pharmacogenetics). Nutritional genomics is a recent off-shoot of this genetic revolution^{2,3} that includes (1) nutrigenomics: The study of interaction of dietary components with the genome, the resulting changes in proteins, and other metabolites; and (2) nutrigenetics: Understanding

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the gene-based differences in response to dietary components and developing nutraceuticals that are most compatible with health for individuals based on their genetic makeup. The area of nutrigenomics has been expanding at a rapid rate in the last decade because of the availability of techniques that can dissect the interaction of nutrients with the genome and subsequent modulation of their effect through transcription factors or membrane-related phenomena. The literature on the ability of dietary fatty acids,^{4,5} soy protein,⁶ and a variety of nutraceutical and herbal compounds⁷⁻¹⁷ to modulate gene expression is vast, and only a few selected references will be mentioned in this review. Elegant research^{6,8,10,11,17} on the molecular interaction of botanicals (ie, resveratrol, phytoestrogens, curcumin, and others) with the genome and their subsequent metabolic effects has given considerable scientific rationale to the areas of herbal medicine and phytotherapy. In this review, some examples will be cited of new opportunities for the functional food and nutraceutical industry to develop products based on individual genetic makeup, which exist not only within the domain of nutrigenetics but also at the nutrigenetic/pharmacogenetic interface.

NUTRIGENETICS

Despite the extensive data on genetic polymorphisms in humans, its translation into medical practice has been slow in view of the time required to accumulate population data on SNP incidence, appreciate the significance of a given SNP in clinical disease, develop suitable diagnostic tests at a reasonable cost, and the physician's ability to offer drug or diet treatment options once the SNP is detected. Therefore, the role of nutrigenetics in direct dietary intervention in humans is only beginning. A few examples that have been successful in demonstrating the potential of nutrigenetics in human health will be cited and opportunities that exist in nutrigenetics to develop nutraceuticals leading to "personalized nutrition" will be discussed. In some instances, potential overlap of nutrigenetics with pharmacogenetics will also become evident, as follows:

1. One of the best-known examples of applicability of nutrigenetics are the 2 SNPs (C677T with a cytosine-to-thymidine substitution resulting in a valine-to-alanine switch and A1298C with adenine-to-cytosine substitution at position 1298 resulting in a glutamic acid-to-alanine switch) in methylene tetrahydrofolate reductase (MTHFR) gene.^{18,19} MTHFR catalyzes the reaction that produces 5-methyl tetrahydrofolate, a cofactor donating a methyl group to a reaction that converts homocysteine to methionine. The presence of either the C677T mutation or the A1298C mutation in com-

ination with C677T mutation in MTHFR gene is associated with reductions in MTHFR enzyme activity. Reduction in MTHFR activity may cause increases in plasma concentration of homocysteine, a risk factor for venous thromboembolic disease, ischemic arterial disease, and neural tube defects.^{20,21} Generally, treating with folic acid supplementation helps to overcome the negative health effect of these SNPs in MTHFR gene.^{22,23}

2. In the cardiovascular disease area, genetic polymorphisms in several key genes have been reported that has bearing on blood lipid levels.²⁴ Except for a few polymorphisms, many of these genetic polymorphisms involve complex relationships and are not yet readily interpretable for direct nutritional intervention. Apolipoprotein E (Apo E) gene polymorphisms consist of 3 different alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$), which are a result of 2 SNPs within exon 4 of the gene. Subjects with the $\epsilon 4$ variant seem to respond to a high-fat diet negatively with an increased risk for coronary heart disease (CHD).^{25,26} In these individuals, a strong dietary recommendation toward a low-fat diet should be useful. In the Framingham Offspring study, interesting differences were noted on the effect of alcohol on low-density lipoprotein (LDL) cholesterol levels in 2 ApoE gene variants,²⁷ with the E2 variant showing lower LDL levels, whereas in E4 subjects, plasma LDL correlated positively with alcohol consumption. With regard to the ApoA1 gene, a G-to-A mutation in the promoter region alters the response to a polyunsaturated diet.²⁸ This difference in the greater amount of a polyunsaturated diet required one to observe an increase in plasma high-density lipoprotein (HDL) levels with a GA genotype (compared with GG genotype) that was noted only in women. From a dietary recommendation point of view, women with this mutation should be counseled to consume higher levels of polyunsaturated fat. The hepatic lipase gene is another promising area that seems to demonstrate differences in terms of plasma HDL levels and response to drugs.²⁹ A mutation in the promoter (C514T) is associated with a difference in response to the level of dietary fat, especially in TT subjects whose HDL levels were high only when consuming <30% energy from fat. Thus, nutritional counseling to reduce the amount of dietary fat in this genotype would be beneficial.
3. Obesity-related genes. Obesity has become a major public health problem in the United States. An intense search has occurred for mutations in obesity-related genes, and this area has been summarized in an excellent review by Loktionov.²⁴ Among potential genes, leptin and leptin receptor

gene mutations have emerged as leading candidates toward predicting obesity.^{30–33} Apart from these genes, studies reporting mutations in the melanocortin 4-receptor and melanocortin 5-receptor genes exist.^{34,35} A study in the Pima, Arizona Indian population³⁶ noted that polymorphisms in noncoding regions of the gene for neuropeptide Y (NPYY5R) receptor gene show strong correlation with the risk of obesity. If these mutations can be identified in families, dietary restriction/intervention based on nutrigenetics starting early in life might be an option to combat obesity.

OPPORTUNITIES FOR NUTRIGENETICS-BASED DIETARY SUPPLEMENTS AND NUTRACEUTICALS IN THE COMPLIMENTARY AND ALTERNATIVE MEDICINE (CAM) ARENA

Dietary supplement and herbal use represents a multi-billion-dollar industry in the United States. In addition, the market for fortified and functional foods globally is projected to grow by at least 7% each year.³⁷ Health food stores and Internet-based retailers offer herbal preparations in capsule, powder, or extract form. The major growth in the dietary supplement industry came after the U.S. Congress passed the Dietary Supplement Health and Education Act of 1994. This law allowed the sale of herbs to help maintain “normal health and physiology” as long as no claims were made to treat a specific disease. A thorough account of the evolution of government regulation as it applies to the sale of nutritional supplements can be found in a review by Buchman.³⁸ Herbal therapies come under the broad umbrella of CAM, which includes acupuncture, homeopathy, and spiritual healing. Although one third of the American population uses some form of CAM, the field is still trying to find its place among Western health-care practitioners. A detailed discussion of CAM, the reasons why it is viewed with skepticism by allopathic physicians, and what it would take to integrate it into the current health-care system can be found in an excellent review by Koretz.³⁹ It seems that 2 serious health concerns^{40,41} exist associated with the use of any herbal preparation at random: (1) Very few herbal preparations have undergone rigorous scientific testing for a specific disease risk, and therefore, a possibility exists that the public may not receive the benefit they are expecting after use; and (2) most herbal extracts represent hundreds of compounds whose effects are unknown and thereby increase the risk of toxicity and interactions with other drugs. A clear example of the difficulty in sorting out the benefits and associated risks in herbal preparations can be found in a review by Wojcikowski et al,⁴² who evaluated potential complementary therapies for chronic kidney disease. It is be-

yond the scope of this review to discuss the extensive literature on the potential interactions of herbs with several commonly used drugs. Clearly, the answer to these concerns rests on purifying active ingredients that can be clinically tested and used as a “nutraceutical” for a specific metabolic problem.

DEVELOPMENT OF NUTRACEUTICALS AT THE NUTRIGENETIC/PHARMACOGENETIC INTERPHASE

In the sections below, opportunities to develop viable nutraceuticals derived from herbs and dietary supplements using information at the nutrigenetic/pharmacogenetic interphase are discussed. The Amazonian herb guarana,⁴³ which is approved as a food additive in the United States, has been chosen to illustrate this point. Extracts of guarana possess strong platelet aggregation inhibition properties,^{44,45} and active principles in this extract can be used toward developing nutraceuticals capable of decreasing the risk of thrombosis, a major risk factor for stroke and CHD in women with genetic mutations.

Many studies have shown that oral contraceptive use in women is associated with increased risk of deep vein thrombosis and stroke.^{46,47} This risk is even greater for those women with prothrombin and factor V Leiden mutations.^{48,49} The response of factor VII to oral contraceptives was also increased with oral contraceptives use.⁵⁰ Recent studies by Kemmeren et al⁵¹ compared oral contraceptives of second (ethinylestradiol/levonorgestrel) and third (ethinylestradiol/desogestrel) generation in women with factor V Leiden mutation and noted higher thrombotic risk in both regimens, with the desogestrel group showing a more pronounced risk. A European case control study⁵² noted that, in women who smoke, oral contraceptives increased the risk of stroke.

Similarly, hormone replacement therapy (HRT) in postmenopausal women has also indicated the negative effects on the risk of stroke and venous thrombosis.^{53,54} A Women’s Health Initiative (WHI) trial using estrogen plus progestin combination reported⁵⁵ a significant increase in the risk of all types of stroke. Cushman et al⁵⁶ reported that estrogen/progestin doubled the risk of stroke and venous thrombosis using the final data from the WHI study. It is interesting to note that increased thrombosis risk was not evident in esterified estrogen (as opposed to conjugated estrogen) used in the WHI study.⁵⁷ Similarly, the negative effect of estrogen therapy on cardiovascular risk was also reported using data derived from the WHI study.^{58–60} The mechanisms involved in the observed increase in thrombosis and cardiovascular events after estrogen therapy are not clear. A recent cross-sectional study⁶¹ of interactions among the thrombophilic factor V Leiden gene muta-

tion, HRT, and CHD in women provides insight into the failure of HRT to reduce CHD in the 3 major trials^{58–60} discussed above. The investigators reported an interaction between HRT-mediated tendency to form blood clots and the factor V Leiden mutation (present in 6% of American women). They speculated that when HRT-mediated thrombophilia is superimposed on the heritable thrombophilic factor V Leiden mutation, CHD is promoted and any putative HRT-associated reduction in CHD is overshadowed. Recently, HRT interaction with another commonly heritable trait, the prothrombin gene mutation, was also suggested.⁶² In women referred for therapy of hyperlipidemia, the authors concluded that when the prothrombin G20210A is absent, HRT is protective against CHD, but in the presence of this mutation, HRT may actually increase the risk for CHD. Similar findings have been reported by Psaty et al.⁶³ These studies suggest that a gene–gender–HRT interaction accounts for increased CHD events in women on HRT, developing from a small subset of women (about 12%), heterozygous for either the factor V Leiden or the prothrombin gene mutations. This interaction could be particularly strong if they are also homozygous for hypofibrinolytic 4G/4G polymorphism of the plasminogen activator inhibitor (PAI)-1 gene, as previous studies have demonstrated that 4G/4G genotype of PAI-1 gene is an independent risk factor for CHD.⁶⁴ These studies strongly support the possibility that the increased risk noted in the WHI trial could be related to thrombophilic mutations in some study participants.

Young women who take oral contraceptives or postmenopausal women on estrogen replacement therapy, especially with the thrombophilic mutations (factor V Leiden, Prothrombin, and PAI-1 mutations), could benefit by preventive dietary or drug therapies that could reduce or control thrombosis risk. Aspirin (a commonly used drug that prevents platelet aggregation and reduces thrombotic risk) and other non-steroidal anti-inflammatory drugs have many side effects, including GI bleeding.⁶⁵ Furthermore, public interest has increased in the use of dietary supplements and availability of well-tested nutraceuticals based on nutrigenetics could help in getting well-tested products for use in individuals with chronic thrombosis risk. In this context, the laboratory focused on exploring potential nutraceuticals from the popular herb guarana (*Paulinia cupana*, *Saponidaceae*). Guarana is a woody spine or sprawling shrub native to the central Amazon Basin.⁴³ In the Amazon region, the fruits of guarana are sundried; its seed are crushed and widely consumed as a high-caffeine stimulant or for medicinal purposes.⁴³ A few carbonated soft drinks containing guarana extract are also popular in Brazil, other Latin American coun-

tries, and more recently, in the United States.^{66,67} According to the natives, guarana is believed to be a source of health and energy and possess “blood-thinning properties.” Studies reported more than a decade ago^{44,45} have noted that aqueous extracts of guarana seeds demonstrated powerful inhibitory properties toward platelet aggregation and thromboxane synthesis. Considering the role of enhanced platelet aggregation and reactivity in thrombosis, inflammation, and pathogenesis of atherosclerosis and stroke,⁶⁸ especially after hormone replacement therapy,⁶⁹ purified guarana preparations could offer considerable benefit as a dietary supplement through reduction in platelet reactivity. In this context, *in vivo* studies are underway in the laboratory using a proprietary subfraction of guarana. This example shows the potential application of nutrigenetics/pharmacogenetics information toward the development of a clinically tested product providing opportunities for nutraceutical and functional food industries.

CONCLUSIONS

Nutrigenetics is a nascent area that is developing quickly and riding on the wave of “personalized medicine” providing opportunities in nutraceutical product development. In this review, the discussion was restricted to a handful of specific genetic polymorphisms in the context of nutrigenetics and metabolic disease. Other important areas exist pertaining to inflammation and oxidative stress that need particular attention in nutrigenetic research in view of their role in many chronic human diseases. A recent review,⁷⁰ for example, discussed the role of oxidative stress in apoptotic pathways in heart disease, clearly suggesting a need for antioxidant supplementation as a preventive therapy. However, nutrigenetic studies are still needed that link specific mutations in the oxidant/antioxidant systems to decreased plasma antioxidant capacity and risk of heart disease. In this manner, specific nutraceuticals (antioxidants) targeted to specific metabolic sites can be developed. Recent interesting research on perilipin gene variation,⁷¹ uncoupling protein 2 genotype,⁷² and ABCG5 polymorphism⁷³ are other examples identifying potential sites for nutraceutical intervention. The ABCG5 genotype, for example, can identify individuals who demonstrate increased response to dietary cholesterol. Following a diet that is rich in ingredients (such as plant sterols) that inhibit cholesterol absorption by these individuals starting early in life might help decrease the magnitude of CHD in this country. Further research on individual differences related to metabolism and requirement of nutrients and genetic profile will help establish nutrigenetics as a discipline that will become an essential part of nutrition and dietetics practice.

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